BeneFIX

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
N/0168	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2020		PL	
II/0164	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/09/2020		SmPC and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

IB/0166/G	This was an application for a group of variations. B.II.z - Quality change - Finished product - Other variation B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.z. - Change in supplier of packaging components or devices (when mentioned in the dossier) - Other variation B.II.g.3 - Deletion of an approved change management protocol related to the finished product	10/09/2020	n/a		
IA/0165	A.7 - Administrative change - Deletion of manufacturing sites	07/08/2020	n/a		
II/0161/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of	25/06/2020	n/a		

	the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol				
II/0163	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	17/04/2020	n/a		
PSUSA/2183/ 201908	Periodic Safety Update EU Single assessment - nonacog alpha	12/03/2020	n/a		PRAC Recommendation - maintenance

II/0160	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	12/09/2019	n/a		
II/0156/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	02/05/2019	n/a		
IB/0159	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	05/04/2019	n/a		
IA/0158	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change	20/03/2019	n/a		

	to an approved stability protocol				
PSUSA/2183/ 201808	Periodic Safety Update EU Single assessment - nonacog alpha	14/03/2019	n/a		PRAC Recommendation - maintenance
IA/0157/G	This was an application for a group of variations. B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	15/02/2019	n/a		
IB/0155/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	03/01/2019	n/a		
IA/0154	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	07/12/2018	19/11/2019	Annex II	

T/0152	Transfer of Marketing Authorisation	11/07/2018	27/09/2018	SmPC, Labelling and PL	
IB/0151/G	This was an application for a group of variations. B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	31/07/2018	n/a		
IB/0150	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	06/07/2018	n/a		
PSUSA/2183/ 201708	Periodic Safety Update EU Single assessment - nonacog alpha	08/03/2018	n/a		PRAC Recommendation - maintenance
IA/0149	A.7 - Administrative change - Deletion of manufacturing sites	13/02/2018	n/a		
IB/0148	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	17/01/2018	n/a		
II/0146	B.II.c.1.d - Change in the specification parameters and/or limits of an excipient - Change outside the approved specifications limits range	26/10/2017	n/a		

IB/0145/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	27/09/2017	n/a		
IA/0144	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	29/06/2017	07/06/2018	SmPC	
IA/0143	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	23/06/2017	n/a		
IB/0142	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	17/05/2017	n/a		
X/0139	Annex I_2.(c) Change or addition of a new strength/potency	26/01/2017	22/03/2017	SmPC, Labelling and	

				PL	
PSUSA/2183/ 201608	Periodic Safety Update EU Single assessment - nonacog alpha	09/03/2017	n/a		PRAC Recommendation - maintenance
II/0138	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	15/12/2016	n/a		
IB/0137/G	This was an application for a group of variations. B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/06/2016	21/10/2016	SmPC, Annex II, Labelling and PL	
IA/0136	A.7 - Administrative change - Deletion of manufacturing sites	16/05/2016	n/a		
PSUSA/2183/ 201508	Periodic Safety Update EU Single assessment - nonacog alpha	17/03/2016	n/a		PRAC Recommendation - maintenance
IB/0135	B.IV.1.z - Change of a measuring or administration device - Other variation	08/01/2016	n/a		
II/0131	Update of section 5.1 of the SmPC with information on once-weakly administration of Benefix based on two open label studies. The RMP has been updated accordingly. Additionally, section 5.2 has been updated with new pharmacokinetic information. The MAH also introduced minor editorial changes	22/10/2015	21/10/2016	SmPC	In this variation the MAH updated the Product Information with data from two open-label studies in which BeneFIX was found to be safely administered at 100 IU/kg once weekly. However, the half-life of the product and the limited pharmacokinetic study data for the once weekly regimen do not allow recommending this regimen in general for long

	throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				term prophylaxis in severe haemophilia B patients.
II/0133	Update of the section 4.8 of the SmPC in order to revise adverse event frequencies based on "all-causality" and "per patient" data set. Update of SmPC sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8 and 4.9 and the corresponding sections of the PL in line with the latest revision of the Core SmPC for Factor IX Products. The RMP version 8.1 has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	20/08/2015	SmPC and PL	In this variation the MAH revised the frequencies of 23 adverse reactions listed in section 4.8 of the SmPC; as a result, 21 of the terms increased in frequency category and 2 ADR terms had frequency categories that remained unchanged. The changes in ADRs frequency were primarily driven by the methodology changes and the enlargement of the data-set, and do not represent a safety signal.
N/0132	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	20/08/2015	PL	
PSUSA/2183/ 201408	Periodic Safety Update EU Single assessment - nonacog alpha	12/03/2015	n/a		PRAC Recommendation - maintenance
II/0126/G	This was an application for a group of variations. Changes to the shelf-life specification of the finished product and to the approved stability protocol of the finished product. B.II.d.1.e - Change in the specification parameters	18/12/2014	n/a		

	and/or limits of the finished product - Change outside the approved specifications limits range B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IA/0129	A.7 - Administrative change - Deletion of manufacturing sites	24/10/2014	n/a		
IB/0128/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	16/10/2014	n/a		
IB/0127	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	14/08/2014	n/a		
II/0119/G	This was an application for a group of variations. B.II.b.5.d - Change to in-process tests or limits applied during the manufacture of the finished product	26/06/2014	n/a		

	- Deletion of an in-process test which may have a significant effect on the overall quality of the finished product B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product				
PSUV/0121	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
IA/0125	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	06/02/2014	n/a		
IA/0124	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	03/02/2014	26/08/2014	Annex II	
IAIN/0122	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	12/12/2013	n/a		
IA/0123	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/12/2013	n/a		
IA/0120	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the	16/10/2013	n/a		

	dossier) - Replacement or addition of a supplier				
IA/0118	A.7 - Administrative change - Deletion of manufacturing sites	23/09/2013	n/a		
II/0117	Update of section 4.8 of the SmPC to include four adverse drug reactions (laryngospasm, wheezing, tremor, and somnolence) in line with the company core data sheet. The Package Leaflet was proposed to be updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/09/2013	26/08/2014	SmPC, Annex II and PL	As a consequence of an internal review, the MAH is correcting inconsistencies regarding the information on adverse Drug Reactions (ADR) between the Core Data Sheet (CDS) and Summary of Product Characteristics (SmPC) of BeneFIX. Laryngospasm and wheezing (as a clinical sign of bronchospasm) were already listed in the PI but not in section 4.8 of the SmPC, tremor and somnolence, were reported in the pivotal studies and in the post-marketing setting and have now been included in section 4.8 of the SmPC.
N/0116	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/07/2013	26/08/2014	PL	
II/0112	Additional storage sites. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	27/06/2013	n/a		
IA/0115	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	17/04/2013	n/a		

IA/0114/G	This was an application for a group of variations. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	14/03/2013	n/a		
II/0111/G	This was an application for a group of variations. Additional test methods for finished product. B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.z - Change in test procedure for the finished product - Other variation	17/01/2013	n/a		
II/0110/G	This was an application for a group of variations. Introduction of alternative test methods for the active substance.	17/01/2013	n/a		

	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0108	Update of sections 4.2 and 5.1 of the SmPC to include information supporting the use of BeneFIX in children less than 6 years of age from Study 3090A1-301-WW and delete the statement that there are insufficient data to support the use of BeneFIX in this patient population. Section 5.2 of the SmPC was also revised to include additional pharmacokinetics parameters in children coming from a pop PK model. The MAH took the opportunity of this variation to bring the PI in line with the latest version of the QRD template (version 8.2) in particular the terms and order in which SOC are presented in section 4.8 of the SmPC. Finally, the MAH updated the contact details of representatives in member states. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	17/01/2013	18/02/2013	SmPC, Annex II and PL	See Scientific Discussion H-139 -VAR- II-108-en.

	modification of an approved one				
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
X/0103	Approval of new strength 3000 IU/vial Annex I_2.(c) Change or addition of a new strength/potency	21/06/2012	23/08/2012	SmPC, Labelling and PL	The new strength of 3000 IU is intended for the following approved indication: treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). The benefix risk profile for the new strength is the same as for the already approved ones.
R/0107	Renewal of the marketing authorisation.	24/05/2012	20/07/2012		Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considers by consensus that the risk-benefit balance of BeneFIX in the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) remains favourable and therefore recommends the renewal of the marketing authorisation.
IG/0169/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	08/06/2012	n/a		

	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0102	Change to active substance manufacturing process. B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	15/03/2012	n/a		
II/0101	Alternative method for active substance batch release testing. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	15/03/2012	n/a		
IB/0106	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	14/02/2012	n/a		
IB/0105	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	23/11/2011	n/a		
T/0100	Transfer of Marketing Authorisation	25/05/2011	23/06/2011	SmPC, Labelling and PL	

WS/0117	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	14/04/2011	31/05/2011	Annex II	
II/0093	Change to raw material used in the active substance manufacturing process. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	14/04/2011	02/05/2011		
IB/0099	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	30/03/2011	n/a	SmPC, Labelling and PL	
IB/0098	C.I.7.z - Deletion of formulation	02/03/2011	n/a	SmPC, Annex II, Labelling and PL	Deletion of the original formulation of Benefix (presentations 001, 002 and 003) which was reformulated and approved as line extension in July 2007 (presentations 004, 005 and 007). The MAH has also taken the opportunity to update Annex IIB in line with the procedural announcement from October and November 2010 regarding the pharmacovigilance system.
II/0088/G	This was an application for a group of variations.	17/02/2011	01/03/2011		

	Changes in the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS				
IB/0097	B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue	25/01/2011	n/a		
N/0096	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2010	n/a	Labelling	
N/0095	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2010	n/a	PL	
IB/0094	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	04/10/2010	n/a		
IB/0091/G	This was an application for a group of variations. To change the storage conditions of the finished product To change the stability protocol	13/08/2010	n/a	SmPC, Labelling and PL	

	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation				
IB/0092	- To change the stability program of the acitve substance B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	08/07/2010	n/a		
S/0084	Annual re-assessment.	18/02/2010	05/05/2010	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk remains favourable and since all specific obligations have been fulfilled, there are no remaining grounds for the Marketing Authorisations to remain under exceptional circumstances.
II/0083	Amendment to drug substance manufacture. Quality changes	22/04/2010	03/05/2010		
IA/0090	To change the current pharmacopeial identification	08/04/2010	n/a		

	test by another pharmacopeial identification test. B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure				
IA/0089/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	08/04/2010	n/a	Annex II	
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/02/2010	n/a	PL	
II/0085	Update of Module 3.2.S 2.3 Control of Starting Material and 3.2. R Regional Information.	21/01/2010	27/01/2010		

	Quality changes				
II/0081	Additional drug product manufacturer. Quality changes	17/12/2009	20/01/2010		Additional drug product manufacturer.
IA/0086	IA_05_Change in the name and/or address of a manufacturer of the finished product	09/12/2009	n/a	Annex II and PL	
II/0082	Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	28/10/2009	SmPC and PL	Following a case of blurred vision reported in the 14th Periodic Safety Update Report (PSUR), the MAH reviewed its safety database and consequently proposed to update the Product Information. Sections 4.4 and 4.8 of the SPC were updated to add "blurred vision" as an early symptom of a hypersensitivity reaction. The Package Leaflet has been updated accordingly.
II/0079	Change in drug substance control assay and specification. Quality changes	24/09/2009	29/09/2009		Change in drug substance control assay and specification.
II/0075	Change to drug substance batch release and stability test method. Quality changes	25/06/2009	16/07/2009		Change to drug substance batch release and stability test method.
II/0077	Changes to QPPV Update of DDPS (Pharmacovigilance)	29/05/2009	30/06/2009	Annex II and PL	Update of the Detailed Description of the Pharmacovigilance System (DDPS) [Module 1.8.1] to reflect a change in the Qualified Person in the EEA for Pharmacovigilance (QPPV). Other administrative and editorial changes are incorporated in this revised DDPS (version 2.1) as well as change in the UK

					local representative.
II/0078	Alternative testing site for one control test of drug product. Quality changes	29/05/2009	16/06/2009		Alternative testing site for one control test of drug product.
IA/0080	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	05/06/2009	n/a		
II/0073	Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/03/2009	22/04/2009	SmPC, Labelling and PL	The MAH proposed to update the SPC, PIL following a review of the pharmacovigilance database, update of the Product Information in line with the company core datasheet version 9.0 and for linguistic improvement. The agreed amendments to the Product Information regarding substantial safety issues include: (1) the risk of thrombosis primarily in neonates together with the risk of administration via continuous infusion (non-approved method of administration) (section 4.4 and 4.8), (2) addition of "bronchospasm" and "laryngospasm" as symptoms of "hypersensitivity reaction" and in section 4.4. (3) and update of "inadequate therapeutic response / factor IX recovery" in section 4.8. Furthermore, the CHMP agreed with MAH to update the section 4.2 of the SPC regarding the administration of BeneFIX by continuous infusion by stating that this is not an approved method of administering the product. Consequently continuous infusion is not recommended.

S/0074	Annual re-assessment.	18/12/2008	23/02/2009	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommends that the marketing authorisation remains under exceptional circumstances. The CHMP agreed with the amendment of annex II of the PI, following the fulfillment of a specific obligation.
II/0070	Modification to the manufacturing process of the drug substance. Quality changes	25/09/2008	01/10/2008		Modification to the manufacturing process of the drug substance.
II/0069	Quality changes	25/09/2008	01/10/2008		
IA/0072	IA_09_Deletion of manufacturing site	12/08/2008	n/a		
IA/0071	IA_27_a_Change to test proc. of immediate packaging - minor change to approved test procedure	07/05/2008	n/a		
II/0068	Quality changes	24/04/2008	28/04/2008		
II/0066	Quality changes	21/02/2008	26/02/2008		
S/0065	Annual re-assessment.	13/12/2007	14/02/2008	SmPC, Annex II and PL	Based on the review of the available information, the CHMP is of the opinion that the quality, safety and efficacy of BeneFIX continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of BeneFIX remains unchanged in the treatment of haemophilia B. Nonetheless, since there are still specific obligations which need to be fulfilled it is recommended that the marketing

					authorisation of BeneFIX remains under exceptional circumstances.
IA/0067	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	20/12/2007	n/a		
II/0064	Update of or change(s) to the pharmaceutical documentation	13/12/2007	19/12/2007		
R/0063	Renewal of the marketing authorisation.	24/05/2007	07/08/2007	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of BeneFIX continues to be favourable. Further to the recent positive opinions granted to the extension applications EMEA/H/C/139/X/55 and X/57, major changes to the formulation of BeneFIX as well as a new higher strength are to be introduced on the market. The safety profile of the new formulation needs to be closely monitored and as there are still ongoing specific obligations, the CHMP recommends that the Marketing Authorisation of BeneFIX remains under exceptional circumstances and that one additional five-year renewal on the basis of pharmacovigilance grounds is required.
X/0057	X-3-iii_Addition of new strength	24/05/2007	30/07/2007	SmPC, Labelling and PL	The Applicant has submitted an extension application to the marketing authorisation for a new strength (2000 IU) of BeneFIX for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Another extension application to the marketing authorisation for a new formulation of BeneFIX was also submitted and

					assessed simultaneously. Based on the provided data on quality, non-clinical and clinical aspects, the benefit risk assessment for reformulated BeneFIX is considered favourable.
X/0055	Annex I_2.(d) Change or addition of a new pharmaceutical form	24/05/2007	30/07/2007	SmPC, Labelling and PL	The MAH has submitted an extension application to the marketing authorisation for a new formulation of BeneFIX for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Another extension application to the marketing authorisation for a new strength (2000 IU) of BeneFIX was also submitted and assessed simultaneously. Based on the provided data on quality, non-clinical and clinical aspects, the benefit risk assessment for reformulated BeneFIX is considered favourable.
II/0060	Quality changes	22/03/2007	02/05/2007	Annex II and PL	
II/0059	Quality changes	22/03/2007	02/04/2007		
S/0058	Annual re-assessment.	14/12/2006	15/02/2007	Annex II and PL	The MAH fulfilled one of their Specific Obligations by completing a new clinical study with BeneFIX in 20 Previously Treated Patients (PTPs) according o the Note for Guidance on FVIII/FIX products CHMP/BPWG/1561/99. Based on the data submitted in this annual re-assessment, the product remains under exceptional circumstances.
IA/0062	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	07/02/2007	n/a		

II/0052	Quality changes	18/10/2006	24/10/2006		
II/0051	Quality changes	21/09/2006	28/09/2006		
II/0050	Quality changes	21/09/2006	28/09/2006		
IA/0053	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	26/06/2006	n/a		
IA/0056	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	22/05/2006	n/a		
II/0049	Update of Summary of Product Characteristics and Package Leaflet	26/01/2006	28/02/2006	SmPC and PL	
II/0048	Update of Summary of Product Characteristics and Package Leaflet	26/01/2006	28/02/2006	SmPC and PL	
II/0045	Quality changes	17/11/2005	23/12/2005	SmPC	
S/0046	Annual re-assessment.	17/11/2005	21/11/2005		Based on the data submitted the product remains under exceptional circumstances.
IB/0047	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	07/10/2005	n/a	SmPC	
II/0043	Update of Summary of Product Characteristics and Package Leaflet	23/06/2005	24/08/2005	SmPC and PL	The MAH applied to update sections 4.2, 4.4, 4.8, 5.2 and 6.6 of the SPC in accordance with the Company Core Data Sheet. The Package Leaflet has been updated accordingly. The data provided by the MAH to support this variation are based on 3 clinical study reports issued following a

					three-segment study: - Pharmacokinetic study in PTPs with severe Hemophilia B (reference C9407-21); - Open label multicentre safety, efficacy and PK study in PTPs with severe and moderate Hemophilia B (References C9407-21 and C9408-21); - Open label multicentre safety and efficacy in PTPs with mild, moderate and severe Hemophilia B during elective surgical procedures (references C9407-21, C9408-21, C9417-21). Section 4.2 posology and method of administration: A minor change in the value of factor IX activity was introduced as well as additional wording to clarify the studied population. The supportive figures are taken from a combination of 2 age groups (15-40 and > 40 years) from studies C9407-21 and C9408-21, respectively. In the clinical studies C9407-21 and C9408-21, Benefix was used in a PTP population. Section 4.4 Special warnings and special precautions for use: The clinical studies performed with BeneFIX did not include sufficient data in the elderly patient population. Further, there are ongoing efficacy and safety studies in the paediatric population. The SPC was updated to reflect this information. Section 4.8 Undesirable effects: - Data on 9 surgery patients from protocol C9417-21 were added to the inhibitor development paragraph in section 4.8 of the SPC. A total of 10 patients were enrolled in this protocol, but one was carried over to protocol C9408-21 and

					is therefore already covered by the current statement in the SPC. These 9 patients meet the same criteria as the 56 already included in this statement, but noone developed inhibitor antibodies to BeneFIX during or after surgery. - In studies C9417-21 and C9408-21 four PTPs experienced a total of 5 e
IA/0044	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	27/06/2005	n/a		
II/0039	Change(s) to the manufacturing process for the active substance	16/03/2005	01/04/2005		
IB/0042	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	23/02/2005	n/a		
IA/0040	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	11/11/2004	n/a	Annex II	
S/0038	7th annual re-assessment	21/10/2004	21/10/2004		Based on the review of all available information, the CHMP is of the view that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of BeneFIX remains favourable in the treatment of haemophilia B. Nonetheless, it is recommended that the marketing authorisation remains under exceptional circumstances until the data requested - the new PTP study, the PUP study and the post-marketing surveillance of all new patients in Europe - are available and assessed (see S/0022). No updating of the SPC or the PL is required as part of this Annual Reassessment.

S/0032	6th Annual Reassessment	26/02/2004	18/08/2004	Annex II	Based on the review of all available information, the CHMP is of the view that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of BeneFIX remains favourable in the treatment of haemophilia B. Nonetheless, it is recommended that the marketing authorisation remains under exceptional circumstances until the data requested are available and assessed (see S/0022). No updating of the SPC or the PL is required as part of this Annual Reassessment.
II/0035	Change(s) to the test method(s) and/or specifications for the active substance	29/07/2004	04/08/2004		
IA/0036	IA_05_Change in the name and/or address of a manufacturer of the finished product	26/07/2004	n/a		
II/0033	Quality changes Quality changes	26/02/2004	05/03/2004		
I/0034	Extension of shelf-life or retest period of the active substance 20a_Extension of shelf-life or retest period of the active substance	03/11/2003	10/11/2003		
II/0029	Quality changes	24/07/2003	04/11/2003		
II/0031	Change(s) to container Change(s) to shelf-life or storage conditions	25/09/2003	02/10/2003		Alternate diluent stopper and extension of the shelf life for the 5 ml diluent sterile water for injections from 18 months to 24 months.

T/0030	Transfer of Marketing Authorisation	21/07/2003	16/09/2003	SmPC, Labelling and PL	The MAH applied for the transfer of the Marketing Authorisation of BeneFIX from Genetics Institute of Europe B.V. to Wyeth Europa Ltd.
R/0024	Renewal of the marketing authorisation.	27/06/2002	03/02/2003	SmPC, Annex II, Labelling and PL	
II/0027	Change(s) to container	21/11/2002	27/11/2002		
I/0028	26_Changes to comply with supplements to pharmacopoeias	15/11/2002	19/11/2002		
II/0025	Change(s) to shelf-life or storage conditions	17/10/2002	28/10/2002		
I/0026	26_Changes to comply with supplements to pharmacopoeias	06/09/2002	24/09/2002		
I/0023	16_Change in the batch size of finished product	27/06/2002	03/07/2002		
II/0021	Update of Summary of Product Characteristics and Package Leaflet	20/09/2001	05/02/2002	SmPC and PL	The MAH applied for a variation to introduce relevant information in the SPC and PL in order to align the SPC for BeneFIX with the core CHMP SPC for "Human Plasma-Derived and Recombinant Coagulation Factor IX Products" (CPMP/BPWG/1625/99), which was part of the MAH's commitments from the 3rd Annual Reassessment. This alignment exercise entails extensive changes to sections 4.1, 4.2, 4.4, 4.8, and 5.2, and minor changes to sections 2, 4.3, 4.5, 4.6, 4.9, 5.1, 5.3, 6.2, 6.4, 6.5 and 6.6. The main changes implemented as a result of this variation are:

					4.1 Therapeutic indications: The current indication has been modified to be in accordance with the core SPC, which refers to prophylaxis in surgical and non-surgical settings. The information regarding treatment of patients with inhibitor is already covered under section 4.2. 4.2 Posology and method of administration: The wording on dosage recommendations (amount and frequency) has been simplified to emphasise the dependence on the clinical effectiveness in each individual. The different ways of expressing Factor IX activity in plasma and the definition of an IU have been inserted in the SPC. The current dosing table for patients with bleeding episodes and/or surgery has been replaced with the table in the core SPC. A sentence stating that there is insufficient data to recommend BeneFIX in children under 6 has been included. A new recommendation to switch patients to another FIX product if doses >100 IU/kg have been repeatedly needed during routine prophylaxis or treatment, even if an inhibitor is not detected, has been included. The information on inhibitors has been simplified and a recommendation to consider alternative therapies in patients with high inhibitor titres included. A number of minor deviations from the core SPC proposed by the MAH in this section are considered acceptable. 4.4 Special warnings and special precautions for use: Statements regarding the lack of established safety and efficacy in
S/0022	4th annual re-assessment	15/11/2001	23/01/2002		The MAH has conducted several studies to investigate the cause for the observed RBC agglutination. The low ionic strength, the most probable cause of RBC agglutination, is

					considered a quality defect of BeneFIX. As an outcome of these investigations the MAH has committed to reformulate the product within agreed timeframes in order to reduce the incidence of RBC agglutination (see also II/0015 & S/0016). The CHMP has recommended intensive post-marketing surveillance for all new patients treated with BeneFIX as well as the initiation of two new studies. The CHMP made this recommendation because GCP inspections of two of the three pivotal clinical studies, on which the Marketing Authorisation is based, revealed deficiencies, which raise doubts on the reliability of the clinical data (see also S/0016). An independent audit of the three clinical studies, commissioned by Genetics Institute, confirmed the GCP deficiencies, but found the data to be representative of the patient population studied. BeneFIX has been commercially available in the United States since 1997 and in the EU since 1999. Post-marketing data accumulated since then from physicians treating haemophilia B patients support the safety and efficacy profile of BeneFIX. The CHMP considers that the benefit/risk balance of BeneFIX for the treatment any prophylaxis of bleeding in previously treated patients (PTPs) with haemophilia B remains positive, basaed on the data presently available. However, the data are insufficient to be certain of the frequency of some adverse drug reactions, especially those linked to inhibitor formation and to allergic reactions. In view of this, there is a need for enhanced surveillance of new patients receiving BeneFIX. This intensive post-marketinig surveillance will include a

					registry for all new patients treated with BeneFIX in Europe, and include careful monitoring for adverse drug reactions. Patients already treated with BeneFIX may continue their therapy, however, pa
II/0018	Update of or change(s) to the pharmaceutical documentation	23/08/2001	25/10/2001		
II/0020	Quality changes	26/07/2001	01/08/2001		
I/0019	12_Minor change of manufacturing process of the active substance	26/04/2001	n/a		
II/0017	Update of Summary of Product Characteristics and Package Leaflet	14/12/2000	23/04/2001	SmPC and PL	The MAH applied for a variation to introduce in the SPC and PL relevant information to address the potentially life-threatening allergic reactions reported by the MAH in the 5th PSUR. Five reports of anaphylactic/ allergic reactions were notified in the reporting interval for the 5th PSUR. Three of these five suspected allergic reactions were potentially life threatening and were considered as class III allergic reactions by the CHMP. The aetiology of the allergic reactions is at present unknown. Although allergic reactions after administration of plasma derived Factor IX are rarely associated with inhibitor formation, it is not known whether patients who experience allergic reactions after treatment with BeneFIX are at increased risk of inhibitor development. Due to the severity of the reactions as well as the unknown aetiology, relevant information has been included in the SPC - sections 4.4 and 4.8 - and the PL, to address the potentially life-threatening allergic reactions reported.

II/0015	Update of Summary of Product Characteristics and Package Leaflet	16/11/2000	23/04/2001	SmPC, Labelling and PL	The MAH applied for a variation to introduce relevant information in the SPC and PL on the red blood cell agglutination phenomenon that had been observed during administration of BeneFIX. In addition, the address of the MAH has been modified and the SPC, PL and labelling amended accordingly. Finally modifications in the instructions to reconstitute and administer the product have been introduced in the PL. Five cases of red cell agglutination - occurring in the line of the tubing and the infusion syringe containing reconstituted BeneFIX and patient's blood - were reported in 2000 and six similar cases were reported in 1997. Following the evaluation of the clinical cases and data from in vitro studies performed to investigate the phenomenon of red cell agglutination (see also S/0022), the CHMP concluded that: - these agglutinates form in the vehicle alone and in non-anticoagulated blood or blood anticoagulated with heparin, EDTA or sodium citrate; - the agglutinates remain quite stable and resistant to dissolution even under venous flow shear rate forces; - in a situation where red cell agglutinates were not permitted to form in the syringe prior to injection, fewer and much shorter red cell aggregates were observed. No clinical sequelae have been reported in association with this observation. If agglutination of red blood cells in the tubing/syringe is observed, all this material (tubing, syringe and BeneFIX solution) should be discarded and

					administration with a new package resumed.
S/0016	3rd annual re-assessment.	25/01/2001	25/01/2001	Annex II	Anaphylactic/allergic reactions, inhibitor development, thrombogenicity and haemorrhage/lack of effect remain areas of relevance. In most cases of allergic reaction no data on inhibitor development are available. Post-marketing studies to evaluate the aetiology of allergic events including anaphylaxis were initiated in 1999. One thrombotic event has been reported after the data lock point for the 5th PSUR as well as several cases of bleeding and/or lack of effect. It is apparent that the doses of BeneFIX required were even higher than those calculated, taking the known difference in recovery of BeneFIX into account. All in all, twelve cases of red cell agglutination in the syringe/tubing system have been reported. The preliminary data suggest that red blood cell agglutination is caused by the BeneFIX vehicle and occur not only in vitro but also when BeneFIX is injected into the flowing blood. Suitable measures will depend on the final assessment of the complete data as requested from the MAH (see also II/0015 & S/0022). There is no evidence of viral transmission for HIV and hepatitis A, B, or C as a result of rFIX treatment. Since the 3rd annual re-assessment, a GCP inspection has been performed. This inspection (Sept 2000) was related to the PUP study (C9418-21) and the CHMP concluded in December 2000 that this study was invalid for regulatory purposes. As a result, the CHMP requested an inspection of the PTP studies (C9407-21 and 49408-21), to be carried out from Jan-March 2001 (see also S/0022).

					The CHMP, having reviewed the evidence of compliance with the Specific Obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendments of the SPC or PL are necessary and that the marketing authorisation remains under exceptional circumstances.
S/0013	Annual re-assessment.	18/11/1999	n/a	Annex II	
I/0012	17_Change in specification of the medicinal product	30/06/1999	n/a		
I/0011	14_Change in specifications of active substance	30/06/1999	n/a		
S/0009	Annual re-assessment.	19/11/1998	29/03/1999	Annex II	
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/02/1999	08/04/1999	PL	
I/0004	03_Change in the name and/or address of the marketing authorisation holder	26/10/1998	11/01/1999	SmPC, Labelling and PL	
I/0007	14_Change in specifications of active substance	08/12/1998	n/a		
I/0006	17_Change in specification of the medicinal product	08/12/1998	n/a		
I/0005	17_Change in specification of the medicinal product	08/12/1998	n/a		
II/0003	Update of Summary of Product Characteristics and Package Leaflet	23/07/1998	11/11/1998	SmPC, Labelling and PL	

I/0008	14_Change in specifications of active substance	09/10/1998	n/a		
I/0001	01_Change following modification(s) of the manufacturing authorisation(s)	22/04/1998	n/a		